ABSTRACT

The present invention provides a metastin derivative having excellent blood stability and exhibiting cancer metastasis inhibiting action or cancer growth inhibiting action. Specifically, the present invention the metastin derivative (I), which is represented by formula:

5

10

15

20

25

30

[wherein, Z^1 , Z^3 , Z^5 and Z^7 represent H or a C_{1-3} alkyl group; Z^2 , Z^4 , Z^6 and Z^8 represent H, O or S; R¹ represents (1) H, or (2) a C₁₋₈ alkyl group optionally substituted with a substituent selected from the group consisting of a carbamoyl group, a hydroxyl group and a aromatic cyclic group; R² represents (1) H or (2) a cyclic or linear C₁₋₁₀ alkyl group, or (3) a C₁₋₁₀ alkyl group consisting of a cyclic alkyl group and a linear alkyl group; R³ represents a C₁₋₈ alkyl group having a basic group, an aralkyl group having a basic group, a C₁₋₄ alkyl group having a non-aromatic cyclic hydrocarbon group of carbon atoms not greater than 7 having a basic group, or a C₁₋₄ alkyl group having a non-aromatic heterocyclic group of carbon atoms not greater than 7 having a basic group; R⁴ represents a C₁₋₄ alkyl group, which may optionally be substituted with a substituent selected from the group consisting of a C₆₋₁₂ aromatic hydrocarbon group, an aromatic heterocyclic group, a C₈₋₁₄ aromatic fused-ring group, an aromatic fused heterocyclic group, a non-aromatic cyclic hydrocarbon group, and a non-aromatic heterocyclic group having carbon atoms not greater than 7; X represents a group shown by formula: -NHCH(Q^1)Y Q^2 C(= Z^9)- (wherein, Q^1 represents a C_{1-4} alkyl group, which may optionally be substituted with a substituent selected from the group consisting of an aromatic hydrocarbon group, an aromatic heterocyclic group, a C₈₋₁₄ aromatic fused-ring group, an aromatic fused heterocyclic group, a non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, and a non-aromatic heterocyclic group having carbon atoms not greater than 7; Q² represents CH₂, NH or O; Y represents -CONH-, -CSNH-, -CH2NH-, -NHCO-, -CH2O-, -CH2S- or -CH₂CH₂-;

Z⁹ represents H, O or S); and P represents (1) H; (2) an optional amino acid residue

continuously or discontinuously bound from the C-terminal end of the 1-48 amino acid sequence in the amino acid sequence represented by SEQ ID NO: 1; (3) a group represented by formula: $J^1-J^2-C(J^3)(Q^3)Y^1C(J^4)(Q^4)Y^2C(J^5)(Q^5)Y^3C(J^6)(Q^6)C(=Z^{10})-$ (wherein, J¹ represents (a) H or (b) (i) a C₁₋₁₅ acyl group, (ii) a C₁₋₁₅ alkyl group, (iii) 5 a carbamoyl group, (iv) a C₁₋₁₅ alkylcarbamoyl group, (v) a C₁₋₁₅ alkanoylcarbamoyl group, (vi) an aminocarbamoyl group, (vii) a C₁₋₁₅ alkylaminocarbamoyl group, (viii) an oxycarbonyl group, (ix) a C₁₋₁₅ alkoxylcarbonyl group, (x) a sulfonyl group, (xi) an amidino group, (xii) a C₁₋₁₅ alkylamidino group, (xiii) a C₁₋₁₅ acylamidino group, (xiv) a C₁₋₁₅ alkylsulfonyl group, or (xv) a oxaryl group, which group may optionally be substituted with cyclic group; J² represents NH, CH₂, O or S; J³ 10 through J⁶ represent H or a C₁₋₃ alkyl group; Q³ through Q⁶ represent a C₁₋₄ alkyl group, which may optionally be substituted with a substituent selected from the group consisting of a C₆₋₁₂ aromatic hydrocarbon group, an aromatic heterocyclic group, a C₈₋₁₄ aromatic fused-ring group, an aromatic fused heterocyclic group, a non-aromatic cyclic hydrocarbon group having carbon atoms not greater than 7, a 15 non-aromatic heterocyclic group having carbon atoms not greater than 7, an amino group, a guanidino group, a hydroxyl group, a carboxyl group, a carbamoyl group, and a sulfhydryl group, or H; J³ and Q³, J⁴ and Q⁴, J⁵ and Q⁵ or J⁶ and Q⁶ may be combined together, or, J² and Q³, Y¹ and Q⁴, Y² and Q⁵, or Y³ and Q⁶ may be combined together, to form a ring; Y¹ through Y³ represent a group represented by 20 formula: $-CON(J^{13})$ -, $-CSN(J^{13})$ -, $-C(J^{14})N(J^{13})$ - or $-N(J^{13})CO$ - (wherein J^{13} and J^{14} represent H or a C₁₋₃ alkyl group); and Z¹⁰ represents H, O or S); (4) a group represented by formula: $J^1-J^2-C(J^7)(Q^7)Y^2C(J^8)(Q^8)Y^3C(J^9)(Q^9)C(=Z^{10})$ - (wherein, J^1 and J² have the same significance as described above; J⁷ through J⁹ have the same significance as J³; O⁷ through O⁹ have the same significance as Q³; Y² and Y³ have 25 the same significance as described above; Z¹⁰ has the same significance as described above; J⁷ and Q⁷, J⁸ and Q⁸ or J⁹ and Q⁹ may be combined together, or, J² and Q⁷, Y² and O⁸ or Y³ and O⁹ may be combined together, to form a ring); (5) a group represented by formula: $J^1-J^2-C(J^{10})(Q^{10})Y^3C(J^{11})(Q^{11})C(=Z^{10})$ - (wherein, J^1 and J^2 have the same significance as described above represents; J^{10} and J^{11} have the same 30 significance as J³; Q¹⁰ and Q¹¹ have the same significance as Q³; Y³ has the same significance as described above; Z¹⁰ has the same significance as described above; and J¹⁰ and O¹⁰ or J¹¹ and O¹¹ may be combined together, or J² and Q¹⁰ or Y³ and Q¹¹ may be combined together, to form a ring); (6) a group represented by formula:

J¹-J²-C(J¹²)(Q¹²)C(=Z¹⁰)- (wherein, J¹ and J² have the same significance as described above; J¹² has the same significance as J³; Q¹² has the same significance as Q³; Z¹⁰ has the same significance as described above; and J¹² and Q¹² may be combined together, or J² and Q¹² may be combined together, to form a ring); or (7) a group represented by formula: J¹- (wherein, J¹ has the same significance as described above)], or a salt thereof.